

Molecular Imaging of Prostate Cancer: Tapping into the Opportunities

Prostate cancer is a major health issue, having the highest incidence rate of all cancers and being the second leading cause of cancer-related deaths in men in the Western world. Because prostate cancer results in substantial morbidity and mortality, it poses a significant burden to a vast number of patients, their caregivers, and the health care system in general. When prostate cancer becomes castration-resistant after failure of hormonal therapy, adequate and accurate imaging procedures are particularly important to guide invasive diagnostic procedures and subsequent therapy. For localized low-volume disease, more sophisticated salvage therapies have been introduced requiring imaging guidance such as high-precision radiotherapy, high-intensity focused ultrasound, and cryosurgery. Similarly, the recent introduction of several novel therapeutics (abiraterone, enzalutamide, sipuleucel-T, cabazitaxel, ^{223}Ra) for advanced stages of disease when prostate cancer has become castration-resistant requires careful selection of patients for optimal, personalized decision making.

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CHOLINE PET/CT

In recent years, several radiopharmaceuticals have been introduced for evaluation of prostate cancer patients by molecular imaging with PET/CT. After the introduction of ^{11}C -labeled choline by Hara et al. (1), the subsequent development of ^{18}F -choline made choline-based PET/CT much more accessible (2), boosting the application for more widespread use in prostate cancer patients. It is of particular importance to progress from feasibility studies in small and often selected patient populations to large clinical studies to assess the strengths and weaknesses of these imaging modalities, adequately positioning them in the diagnostic armamentarium.

Two metaanalyses evaluated choline PET and PET/CT in castration-resistant prostate cancer patients with biochemical failure after curative local treatment (3,4). Evangelista et al. evaluated 19 studies on 1,555 patients. They showed a pooled sensitivity and specificity for disease (local recurrence, lymph nodes, and bone) of 85.6% and 92.6%, respectively (3). Umbehr et al. reported similar results from 12 studies on 1,055 patients (4). Both

studies noted the importance of prostate-specific antigen (PSA), PSA doubling time, and PSA velocity. In a third metaanalysis of 14 mostly retrospective studies on a total of 1,869 patients, Treglia et al. reported a pooled detection rate of 58% for choline PET/CT in restaging castration-resistant prostate cancer. They emphasized the importance of PSA levels and especially PSA kinetics for the tumor detection rate. A PSA doubling time of less than 6 mo and PSA velocity of more than 1 ng/mL/y or more than 2 ng/mL/y proved to be relevant factors in predicting the positive result of choline PET/CT (5). The role of PSA level at initiation of the choline PET/CT study influenced the detection rates in recurrent prostate cancers after surgery versus radiotherapy because of differences in the definition of recurrent prostate cancer; that is, postsurgery PSA greater than 0.2 ng/mL versus PSA nadir + 2 ng/mL after radiotherapy.

In this issue of *The Journal of Nuclear Medicine*, Cimitan et al. report the results of ^{18}F -choline PET/CT in a cohort of 1,000 prostate cancer patients with biochemical recurrence after potentially curative surgery or radiotherapy (6). Despite being retrospective and observational, with the inherent methodologic limitations, this study made several clinically relevant observations on this large patient group. In two thirds of the patients, ^{18}F -choline PET/CT detected the source of the PSA rise, approximately evenly distributed between local recurrence, lymph node metastases, and distant metastases. In line with earlier observations (5), a clear relation was confirmed between the detection rate of disease and PSA levels and PSA velocity, up to 79% when PSA was higher than 2 ng/mL. However, even when PSA was below 1 ng/mL or between 1 and 2 ng/mL, detection rates for ^{18}F -choline PET/CT were still considerable (31% and 43%, respectively). In all subgroups, the detection rate was highest in those patients who were initially diagnosed with a Gleason score of 7 or higher, as demonstrated by multivariate analysis. This observation is important because it may modify current clinical practice, as a PSA level higher than 1 or even 2 ng/mL is often used as a cutoff to refer patients for ^{18}F -choline PET/CT. Cimitan et al. provide evidence that ^{18}F -choline PET/CT should also be considered at low PSA levels in the case of a Gleason score above 7 at initial diagnosis (6).

PATIENT SELECTION WITH CHOLINE PET/CT

Recent clinical studies showed that 60 patients with biochemical progression after radical prostatectomy and selected for high-dose salvage radiation therapy with ^{18}F -choline PET/CT had a 3-y biochemical progression-free survival rate of 72.5% (7). Still, as recurrent prostate cancer after radical surgical treatment is diagnosed by a PSA level of more than 0.2 ng/mL, the added clinical value of choline PET/CT imaging in patients with such low PSA levels remains limited. Salvage radiotherapy will start at PSA levels of between 0.2 and 0.3 ng/mL, at which level the detection rates of any type of imaging will be too low for routine use. In 52

Received Dec. 1, 2014; revision accepted Dec. 2, 2014.

For correspondence or reprints contact: Wim J.G. Oyen, Department of Radiology and Nuclear Medicine, Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

E-mail: wim.oyen@radboudumc.nl

Published online Dec. 31, 2014.

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DOI: 10.2967/jnumed.114.150219

prostate cancer patients who underwent salvage lymph node dissection for nodal recurrence detected by ^{11}C -choline PET/CT, Karnes et al. reported a 3-y biochemical recurrence-free, systemic progression-free, and cancer-specific survival of 45.5%, 46.9%, and 92.5%, respectively (8). At present, choline PET/CT raises considerable interest as reflected by more than 20 trials listed at clinicaltrials.gov. Large-scale prospective clinical trials using choline PET/CT are eagerly awaited.

OTHER RADIOPHARMACEUTICALS

Acknowledging that the role of ^{18}F -FDG PET/CT is rather limited in prostate cancer as compared with other cancer types, several other radiopharmaceuticals have been proposed for molecular imaging of castration-resistant prostate cancer. Prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein overexpressed on prostate cancer cells, proved to be an important target since the introduction of ^{111}In -capromab pendetide (ProstaScint; Cytogen Corp.), a mouse monoclonal antibody that recognizes an intracellular domain of PSMA. Given the well-known disadvantages of antibodies (e.g., long interval between injection and imaging, relatively low lesion-to-background ratios, immunogenicity of the agent) and the advantages of PET over SPECT, the development of PSMA-targeting small molecules labeled with PET radionuclides was a logical and important step. Several PSMA-targeting peptides have been developed and some translated to clinical studies. First studies with ^{68}Ga -labeled HBED-CC (*N,N'*-bis-[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-*N,N'*-diacetic acid) PSMA PET/CT indicate its potential as a powerful diagnostic agent showing higher lesion detection rates than ^{18}F -choline PET/CT (9). As compared with PET/CT, PET/MR imaging with ^{68}Ga -PSMA peptides may further improve diagnostic accuracy because of easier and more accurate detection of lesions (10).

Other radiopharmaceuticals are also under development, such as the amino acid analog anti-3- ^{18}F -fluorocyclobutane, which exploits the overexpression of the alanine-serine-cysteine transport system in prostate cancer. An early PET/CT clinical study reported an approximately 60% higher lesion detection rate by anti-3- ^{18}F -fluorocyclobutane than by ^{11}C -choline (11). Given the pivotal role of the androgen receptor in prostate cancer, ^{18}F -fluorodihydrotestosterone may also become a radiopharmaceutical that can stratify patients for optimal selection of treatment by assessing the presence and modulation of the receptor before and during antiandrogenic treatment.

CONCLUSION

Using clinical, histologic, and laboratory data to optimize the appropriate use of novel radiopharmaceuticals is important to minimize the application in patient groups in which the diagnostic yield is low. It is of equal importance to identify those individuals within low-yield groups who do have additional risk factors that increase the likelihood of positive, management-changing imaging procedures. This is underlined by the study of Cimitan et al. suggesting that high initial Gleason scores identify patients with PSA levels of between 1 and 2 ng/mL in whom a positive ^{18}F -choline PET/CT result is more likely (6). In order to progress to evidence-based inclusion in guidelines,

these data support the step from descriptive patient studies toward prospective clinical studies with a significant impact on individualized patient management in clinical practice, addressing the impact on patient management, treatment selection, patient outcome, quality of life, and cost-effectiveness of ^{18}F -choline PET/CT. Performing those trials that anchor our procedures in general clinical practice is at least as important as tapping into the many opportunities provided by the wealth of newly developed radiopharmaceuticals that are currently being translated to early clinical studies in patients with castration-resistant prostate cancer.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

Wim J.G. Oyen

*Radboud University Medical Center
Nijmegen, The Netherlands*

Igle J. De Jong

*University Medical Center Groningen
Groningen, The Netherlands*

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